

General

Guideline Title

2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis.

Bibliographic Source(s)

Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St Clair EW, Tindall E, Miller AS, McAlindon T, American College of Rheumatology. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2016 Jan;68(1):1-25. [160 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, Bridges SL Jr, Chatham WW, Paulus HE, Suarez-Almazor M, Bombardier C, Dougados M, Khanna D, King CM, Leong AL, Matteson EL, Schousboe JT, Moynihan E, Kolba KS, Jain A, Volkmann ER, Agrawal H, Bae S, Mudano AS, Patkar NM, Saag KG. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012 May;64(5):625-39.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report [Clinical Practice Guidelines We Can Trust](#).

■■■■= Poor ■■■= Fair ■■■= Good ■■■= Very Good ■■■= Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source

	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
UNKNOWN	Multidisciplinary Group
YES	Methodologist Involvement
	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
	Search Strategy
	Study Selection
	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
	Grading the Quality or Strength of Evidence
	Benefits and Harms of Recommendations
	Evidence Summary Supporting Recommendations
	Rating the Strength of Recommendations
	Specific and Unambiguous Articulation of Recommendations
	External Review
	Updating

Recommendations

Major Recommendations

The strength of the recommendation (strong, conditional) is defined at the end of the "Major Recommendations" field. Strong recommendations are bolded and conditional recommendations are italicized. Refer to Figures 2, 4, and 7 in the original guideline document for the levels of evidence supporting each recommendation.

Note on recommendations for laboratory monitoring for disease-modifying antirheumatic drugs (DMARDs) and tuberculosis (TB) screening in patients receiving biologics or tofacitinib: The panel endorsed the recommendations previously published in the 2008 recommendations and in the 2012 update to be included in the 2015 recommendations (see Table 3 and Figure 6 in the original guideline document). The panel indicated that in the absence of significant new knowledge, development of an alternate recommendation was not warranted with one exception: the Voting Panel recommended that the same TB screening algorithm as described for biologics should be followed for patients receiving tofacitinib. For additional details (including baseline laboratory monitoring), please see the [2008](#)

Recommendations for Early Rheumatology Rheumatoid (RA) Patients

The authors strongly recommend using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, another target may be chosen because risk tolerance by patients or comorbidities may mitigate the usual choices. For disease-modifying antirheumatic drug (DMARD)-naïve patients with early, symptomatic RA, the authors strongly recommend DMARD monotherapy over double or triple DMARD therapy in patients with low disease activity and *conditionally recommend DMARD monotherapy over double or triple DMARD therapy in patients with moderate or high disease activity*. Methotrexate should be the preferred initial therapy for most patients with early RA with active disease. For patients with moderate or high disease activity despite DMARD therapy (with or without glucocorticoids), the authors strongly recommend treatment with a combination of DMARDs or a tumor necrosis factor inhibitor (TNFi) or a non-TNF biologic, with or without methotrexate (MTX) in no particular order of preference, rather than continuing DMARD monotherapy alone. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to superior efficacy.

For patients with moderate or high disease activity despite any of the above DMARD or biologic therapies, the authors conditionally recommend adding low-dose glucocorticoids (defined as ≤ 10 mg/day of prednisone or equivalent). Low-dose glucocorticoids may also be used in patients who need a bridge until realizing the benefits of DMARD therapy. The risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and the duration of therapy is short.

For patients experiencing a flare of RA, the authors conditionally recommend adding short-term glucocorticoids (<3 months of treatment) at the lowest possible dose for the shortest possible duration, to provide a favorable benefit-risk ratio for the patient.

Recommendations for Established RA Patients

The authors strongly recommend using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, however, another target may be chosen because tolerance by patients or comorbidities may mitigate the usual choices. For DMARD-naïve patients with low disease activity, the authors strongly recommend using DMARD monotherapy over a TNFi. *For DMARD-naïve patients with moderate or high disease activity, the authors conditionally recommend DMARD monotherapy over double or triple DMARD therapy and DMARD monotherapy over tofacitinib*. In general, MTX should be the preferred initial therapy for most patients with established RA with active disease. For patients with moderate or high disease activity despite DMARD monotherapy including methotrexate, the authors strongly recommend using combination DMARDs or adding a TNFi or a non-TNF biologic or tofacitinib (all choices with or without methotrexate) in no particular order of preference, rather than continuing DMARD monotherapy alone. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to its superior efficacy.

For all scenarios for established RA below, treatment may be with or without MTX.

For moderate or high disease activity despite TNFi therapy in patients currently not on a DMARD, the authors strongly recommend that one or two DMARDs be added to TNFi therapy rather than continuing TNFi therapy alone.

If disease activity is moderate or high despite single TNFi biologic therapy, the authors conditionally recommend using a non-TNF biologic.

If disease activity is moderate or high despite non-TNF biologic therapy, the authors conditionally recommend using another non-TNF biologic. However, if a patient has failed multiple non-TNF biologics and they are TNFi-naïve with moderate or high disease activity, the authors conditionally recommend treatment with a TNFi.

For patients with moderate or high disease activity despite prior treatment with at least one TNFi and at least one non-TNF-biologic (sequentially, not combined), the authors conditionally recommend first treating with another non-TNF biologic. However, when a non-TNF biologic is not an option (e.g., patient declines non-TNF biologic therapy due to inefficacy or side effects), the authors conditionally recommend treatment with tofacitinib.

If disease activity is moderate or high despite the use of multiple (2+) TNFi therapies (in sequence, not concurrently), the authors conditionally recommend non-TNF biologic therapy and then conditionally treating with tofacitinib when a non-TNF biologic is not an option.

If disease activity is moderate or high despite any of the above DMARD or biologic therapies, the authors conditionally recommend adding low-dose glucocorticoids.

If patients with established RA experience an RA flare while on DMARD, TNFi, or non-TNF biologic therapy, the authors conditionally recommend adding short-term glucocorticoids (<3 months of treatment) at the lowest possible dose and for shortest possible duration to provide the best benefit-risk ratio for the patient.

In patients with established RA and low disease activity but not remission, the authors strongly recommend continuing DMARD therapy, TNFi, non-TNF biologic or tofacitinib rather than discontinuing respective medication.

In patients with established RA currently in remission, the authors conditionally recommend tapering DMARD therapy, TNFi, non-TNF biologic, or tofacitinib.

The authors strongly recommend not discontinuing all therapies in patients with established RA in disease remission.

Recommendations for RA Patients with High-Risk Comorbidities

Congestive Heart Failure (CHF)

In patients with established RA with moderate or high disease activity and New York Heart Association (NYHA) class III or IV CHF, the authors conditionally recommend using combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a TNFi.

If patients in this population are treated with a TNFi and their CHF worsens while on the TNFi, the authors conditionally recommend switching to combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a different TNFi.

Hepatitis B

In patients with established RA with moderate or high disease activity and evidence of active hepatitis B infection (hepatitis surface antigen positive >6 months), who are receiving or have received effective antiviral treatment, the authors strongly recommend treating them the same as patients without this condition.

For a patient with natural immunity from prior exposure to hepatitis B (i.e., HB core antibody and hepatitis B surface [HBS] antibody positive and normal liver function tests), the authors recommend the same therapies as those without such findings as long as the patient's viral load is monitored. For patients with chronic hepatitis B who are untreated, referral for antiviral therapy is appropriate prior to immunosuppressive therapy.

Hepatitis C

In patients with established RA with moderate or high disease activity and evidence of chronic hepatitis C virus (HCV) infection, who are receiving or have received effective antiviral treatment, the authors conditionally recommend treating them the same as the patients without this condition. The authors recommend that rheumatologists work with gastroenterologists and/or hepatologists who would monitor patients and reassess the appropriateness of antiviral therapy. This is important considering the recent availability of highly effective therapy for HCV, which may lead to a greater number of HCV patients being treated successfully.

If the same patient is not requiring or receiving antiviral treatment for their hepatitis C, the authors conditionally recommend using DMARD therapy rather than TNFi.

Malignancy

Previous Melanoma and Non-melanoma Skin Cancer

In patients with established RA and moderate or high disease activity and a history of previously treated or untreated skin cancer (melanoma or non-melanoma), the authors conditionally recommend the use of DMARD therapy over biologics or tofacitinib.

Previous Lymphoproliferative Disorders

In patients with established RA with moderate or high disease activity and a history of a previously treated lymphoproliferative disorder, the authors strongly recommend using rituximab rather than a TNFi and conditionally recommend using combination DMARD therapy, abatacept or tocilizumab rather than TNFi.

Previous Solid Organ Cancer

In patients with established RA with moderate or high disease activity and previously treated solid organ cancer, the authors conditionally recommend that they be treated for RA just as one would treat an RA patient without a history of solid organ cancer.

Serious Infections

In patients with established RA with moderate or high disease activity and previous serious infection(s), the authors conditionally recommend using combination DMARD therapy or abatacept rather than TNFi.

Recommendations for the Use of Vaccines in RA Patients on DMARD and/or Biologic Therapy

In early or established RA patients aged 50 and over, the authors conditionally recommend giving the herpes zoster vaccine before the patient receives biologic therapy or tofacitinib for their RA.
In early or established RA patients who are currently receiving biologics, the authors conditionally recommend that live attenuated vaccines such as the herpes zoster (shingles) vaccine not be given .
In patients with early or established RA who are currently receiving biologics, the authors strongly recommend using appropriately indicated killed/inactivated vaccines.

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group Grades of Evidence

High Quality: Further research is very unlikely to change confidence in the estimate of effect.

Moderate Quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low Quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very Low Quality: Any estimate of effect is very uncertain.

Strength of the Recommendation

A strong recommendation (in bold face above) means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation.

A conditional recommendation (in italics above) means that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this,

conditional recommendations are preference sensitive and always warrant a shared decision-making approach.

Implications of Strong and Conditional GRADE Methodology Recommendations

	Strong recommendation	Conditional recommendation
Patients	Most people in your situation would want the recommended course of action and only a small proportion would not	The majority of people in your situation would want the recommended course of action, but many would not*
Clinicians	Most patients should receive the recommended course of action	Be prepared to help patients to make a decision that is consistent with their own values
Policy makers	The recommendation can be adapted as a policy in most situations	There is a need for substantial debate and involvement of stakeholders

*Majority means >50% of the people

Clinical Algorithm(s)

The following clinical algorithms are provided in the original guideline document:

2015 American College of Rheumatology (ACR) recommendations for the treatment of early rheumatoid arthritis (RA), defined as a disease duration <6 months

2015 ACR recommendations for the treatment of established RA, defined as a disease duration ≥6 months, or meeting the 1987 ACR classification criteria

Tuberculosis (TB) screening algorithm for biologics or tofacitinib (endorsed and modified from the 2012 American College of Rheumatology RA treatment recommendations)

Scope

Disease/Condition(s)

Rheumatoid arthritis (RA) (early [<6 months] or established [≥6 months or meeting 1987 American College of Rheumatology RA classification criteria])

Guideline Category

Evaluation

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Rheumatology

Intended Users

Advanced Practice Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

- To develop a new evidence-based, pharmacologic treatment guideline for rheumatoid arthritis (RA)
- To serve as a tool for clinicians and patients (the two target audiences) for pharmacologic treatment decisions in commonly encountered clinical situations

Target Population

- Adult patients with early or established rheumatoid arthritis (RA)
- Adult patients with RA and high-risk comorbidities including congestive heart failure, hepatitis B or C, previous malignancies, or previous serious infections

Interventions and Practices Considered

1. Use of a treat-to-target strategy rather than a non-targeted approach
2. Nonbiologic disease-modifying antirheumatic drugs (DMARDs)
 - DMARD monotherapy
 - Methotrexate (MTX)
 - Leflunomide (LEF)
 - Hydroxychloroquine (HCQ)
 - Sulfasalazine (SSZ)
 - Double DMARD therapy (MTX + SSZ, MTX + HCQ, SSZ + HCQ, or combinations with LEF)
 - Triple DMARD therapy (MTX + SSZ + HCQ)
 - DMARD combination therapy
3. Biologics
 - Tumor necrosis factor inhibitor (TNFi) biologics (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab)
 - Non-TNF biologics (abatacept, rituximab, or tocilizumab)
4. Tofacitinib
5. Glucocorticoids (prednisone or equivalent)
6. Use of vaccines in patients receiving DMARDs and/or biologics
7. Tuberculosis (TB) screening for patients receiving biologic DMARDs and tofacitinib
8. Treatment considerations for patients with high-risk comorbidities (congestive heart failure, hepatitis B or C, previous malignancies, or previous serious infections)
9. Laboratory monitoring for traditional DMARDs

Major Outcomes Considered

- Rheumatoid arthritis (RA) disease activity as measured by American College of Rheumatology (ACR) 70, ACR 50 or ACR 20 response, Disease Activity Score (DAS-28), or other scoring systems
- Health Assessment Questionnaire-Disability assessment (HAQ-DI) scores (measures of physical function/physical disability)
- Percent of patients with detectable radiographic progression (assessed using total Sharp score or Larsen radiographic progression score)
- Study withdrawals due to adverse events
- Gastrointestinal, hepatic, neurological, pulmonary, and cardiovascular toxicities of treatment

- Infections
- Hypertension
- Malignancies
- Infusion or injection site reactions
- Osteoporosis or osteoporotic fractures
- Mortality

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Searches

The authors performed systematic searches of the published literature to identify relevant evidence for the PICO (population, intervention, comparator, and outcomes) questions. Study designs in the literature review included systematic reviews, randomized controlled trials (RCTs), and observational studies (including case series). The authors searched OVID Medline, PubMed, EMBASE, and the Cochrane Library (including Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; Cochrane Central Register of Controlled Trials; and Health Technology Assessments) (see Supplementary Appendix 2 of the original guideline document [see the "Availability of Companion Documents" field]). The searches were performed using database-specific subject headings and keywords related to the following domains of interest: rheumatoid arthritis (RA), traditional/conventional disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor inhibitor (TNFi) biologics (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab), non-TNF biologics (abatacept, rituximab, or tocilizumab), tofacitinib, glucocorticoids, and adverse events. Searches were limited to adults ages ≥ 18 years and to English language publications. Duplicate references were removed. The authors excluded narrative reviews, editorials, scientific conference abstracts, and case reports.

The literature related to treatment modalities covered by past American College of Rheumatology (ACR) RA guidelines (i.e., traditional/conventional DMARDs, TNFi and non-TNF biologics) and tofacitinib was searched to include articles published from January 1, 2009 through March 3, 2014. For other treatment modalities not covered by past ACR RA guidelines (i.e., glucocorticoids), the authors searched the databases from inception until March 3, 2014. Initial literature searches were updated on September 17, 2014. All searches were developed by a medical librarian in collaboration with the Literature Review Team and were peer reviewed by a second medical librarian.

Study Selection

The literature search results underwent primary screening in DistillerSR software (Evidence Partners). During primary literature screening, 2 reviewers (various pairs, made from a pool of reviewers including authors, as well as the medical librarian) independently reviewed the title and abstract of each article for potential eligibility. A third reviewer resolved conflicts regarding inclusion versus exclusion. Articles judged as potentially eligible were tagged for electronic matching to specific PICO questions, and subsequently underwent full-text article screening. Each full text was screened by 2 reviewers and independently tagged with PICO-matching criteria. A secondary hand sorting of all randomized studies was conducted to ensure successful matching of relevant evidence to PICO questions (for details on the

study selection see Supplementary Appendix 3 of the original guideline document [see the "Availability of Companion Documents" field]).

Number of Source Documents

A total of 108 studies were included in the evidence report.

Refer to Supplementary Appendix 3 of the original guideline document (see also the "Companion Documents" field) for a flowchart of the study selection process.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group Grades of Evidence

High Quality: Further research is very unlikely to change confidence in the estimate of effect.

Moderate Quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low Quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very Low Quality: Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Analysis

The authors extracted study data for each PICO (population, intervention, comparator, and outcomes) question into RevMan software. When determining which data to include, they followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology that gives preference to randomized controlled trials (RCTs) over observational studies as the highest-quality source of evidence. Whenever data from both randomized and observational trials were available, and the RCT was of high quality, the authors extracted RCT data only. A RevMan file was created for each PICO question, and data were pooled and analyzed using this software. Continuous outcome variables were analyzed using the inverse variance method in a random effects model. Continuous outcomes were reported as mean differences with 95% confidence intervals; standardized mean differences (similar in concept to effect sizes) were used when the outcome was measured with different scales. Dichotomous variables were analyzed using the Mantel-Haenszel method in a random effects model. These variables were reported as risk ratios with 95% confidence intervals.

Quality Assessment and Evidence Report Formulation

The authors exported RevMan analyses into GRADEpro software to formulate a GRADE summary of findings table for each PICO question. The quality of evidence, such as the confidence in the effect

estimates for each outcome, was evaluated based on GRADE quality assessment criteria. Two independent reviewers performed this GRADE quality assessment in duplicate and discordance was resolved by consensus. This included the risk of bias in included trials, the likelihood of publication bias, inconsistency between trial results, indirectness of the evidence (e.g., differences between populations, interventions, or outcomes of interest in the group to whom the recommendation applies versus those who were included in the studies referenced), and imprecision (wide confidence intervals, usually due to a small number of patients or events, or those situations where clinical decision-making would differ at the extremes of the confidence interval).

The GRADE method distinguishes 4 levels of quality of evidence based on the degree of confidence that the pooled effect estimate lies close to the true effect. Thus, the quality of evidence for each outcome could be rated as high, moderate, low, or very low. The overall evidence quality grade was the lowest quality rating among the individual outcomes deemed critical for the comparison between interventions. In the absence of any data, the level of evidence was rated as very low, because it was based on clinical experience only.

The authors compiled the resulting summary of findings tables in an evidence report (see Supplementary Appendix 1 in the original guideline document [see the "Availability of Companion Documents" field]) that was accompanied by a qualitative summary of the evidence for each PICO question. The Content Panel reviewed the drafted evidence report and revised the report to address evidence gaps prior to presentation to the Voting Panel. The authors referred to other society/organization guidelines for topics that do not exclusively relate to rheumatologic care, such as liver disease (American Association for the Study of Liver Diseases [AASLD]) and TB screening and immunization (Centers for Disease Control and Prevention [CDC]).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overall Methodology

This guideline was developed following the recently revised American College of Rheumatology (ACR) guideline development process (<http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines> [redacted]). This process includes the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (available at www.gradeworkinggroup.org [redacted]).

Teams Involved

A Core Leadership Team supervised the project and was responsible for defining the project scope, drafting the clinical questions to be addressed by the guideline, coordinating with the Literature Review Team's efforts, and drafting the manuscript based on voting by a panel (described below). The Core Leadership Team was led by a chair who possessed both content and methodologic expertise. The Core Leadership Team also included a methodologist, who advised on the process and provided input on the GRADE summary of findings tables, and experts in guideline development. A Literature Review Team conducted the literature review, graded the quality of evidence, developed the summary of findings tables, and produced an evidence report. A Content Panel, composed of 4 content experts reviewed and provided feedback on the clinical questions and the evidence report, and provided consultation throughout the project. Finally, a Voting Panel helped determine which clinical questions would be asked and which outcomes were critical, and they voted on the final recommendations after reviewing the evidence provided by the Literature Review Team. The Voting Panel included rheumatologists with expertise and clinical experience in treating rheumatoid arthritis, as well as 2 patient representatives. Training was conducted with all members of the guideline development group to prepare them for their roles, including

specific sessions on the ACR guideline process and GRADE methodology.

Establishing Key Principles and PICO (Population, Intervention, Comparator, and Outcomes) Development

Key principles and provisos, key terms, descriptions, and drug categories used in the guideline development process are shown in Table 1 of the original guideline document. These key principles were first reviewed by the Content Panel and the Core Leadership Team. The key principles were then provided to the Voting Panel when they reviewed the drafted evidence report, and also when they discussed and voted on each recommendation. The Core Leadership Team collaborated with the Content Panel to develop the initial set of PICO-formatted clinical questions for the guideline. The authors considered clinically relevant interventions and comparators after extensive discussion with the Content Panel and the Core Leadership Team, balancing comprehensiveness with feasibility. These PICO questions were posted for 30 days on the ACR Web site for public comment, and revised accordingly. The final set of PICO questions addressed 6 major topics.

Moving from Evidence to Recommendations

Each recommendation was made based on a consideration of the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the effect estimates), and patients' values and preferences, as per GRADE methodology. A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention far outweigh the harms (or vice versa) (see the "Rating Scheme for the Strength of the Recommendations" field). A conditional recommendation denotes uncertainty over the balance of benefits and harms, such as when the evidence quality is low or very low, or when patient preferences or costs are expected to impact the decision. Thus, conditional recommendations refer to decisions where incorporation of patient preferences is an essential element of decision making.

Consensus Building

The Voting Panel received the evidence report for review before it met to discuss and decide on the final recommendations. For each PICO question, the Voting Panel heard an oral summary of the evidence and provided votes on the direction and strength of the related recommendation during a face-to-face meeting held on October 5–6, 2014, and subsequent conference calls and e-mails. The voting process was anonymous and conducted using Poll Everywhere software (available at www.poll.everywhere.com). The authors used the 70% consensus threshold, which has been used previously in other similar processes and in previous ACR guidelines. If 70% consensus was not achieved during an initial vote, the panel members held additional discussions before voting again. In some instances (specifically, disease-modifying antirheumatic drug [DMARD] monotherapy failure in early and established rheumatoid arthritis, hepatitis B, hepatitis C, and previously treated/untreated solid organ cancer), the Voting Panel decided, based on its review of the evidence and its round 1 votes, to combine certain treatment options. They then voted on a new recommendation statement that covered a group of treatment options instead of considering each question separately. In addition, the Voting Panel dropped a number of PICO questions because the clinical scenario was uncommon, irrelevant, or redundant (see Supplementary Appendix 4 of the original guideline document [see the "Availability of Companion Documents" field]).

The GRADE methodology contributed a great deal of transparency to the voting process. For example, all of the evidence tables contained detailed descriptions of the criteria upon which the evidence quality was rated (such as estimates of risk of bias or indirectness). As allowed for in GRADE, in some instances, the Voting Panel chose to provide a recommendation in disagreement with the expected strength based on the overall evidence quality (i.e., a strong recommendation despite a low quality rating of evidence). In such cases, a written explanation was provided describing the reasons behind this decision.

Rating Scheme for the Strength of the Recommendations

Strength of the Recommendation

A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. A conditional recommendation means that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach.

Implications of Strong and Conditional GRADE Methodology Recommendations

	Strong recommendation	Conditional recommendation
Patients	Most people in your situation would want the recommended course of action and only a small proportion would not	The majority of people in your situation would want the recommended course of action, but many would not*
Clinicians	Most patients should receive the recommended course of action	Be prepared to help patients to make a decision that is consistent with their own values
Policy makers	The recommendation can be adapted as a policy in most situations	There is a need for substantial debate and involvement of stakeholders

*Majority means >50% of the people

Cost Analysis

Cost is a consideration in these recommendations; however, explicit cost-effectiveness analyses were not conducted.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Final Review and Approval of the Manuscript by the American College of Rheumatology (ACR)

In addition to journal peer review, the manuscript was reviewed by the ACR Guideline Subcommittee, ACR Quality of Care Committee, and the ACR Board of Directors, a process that involved over 40 reviewers (details available at www.rheumatology.org). These ACR oversight groups did not mandate that certain recommendations be made within the guideline, but rather, these ACR committees served as peer reviewers.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field). Refer to Figures 2, 4, and 7 in the original guideline document for the levels of evidence supporting each recommendation.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate use of pharmacologic treatment for patients with early rheumatoid arthritis (RA), established RA, and high-risk comorbidities (i.e., hepatitis, congestive heart failure, malignancy, and/or serious infections)
- Appropriate screening for tuberculosis, use of vaccines, and laboratory monitoring

Refer to the original guideline document and to Supplementary Appendix 1 (see the "Availability of Companion Documents" field) for specific benefits of the recommendations.

Potential Harms

Adverse effects of pharmacologic treatment (i.e., disease-modifying antirheumatic drugs [DMARDs], biologic agents, tofacitinib, and glucocorticoids)

Refer to the original guideline document and to Supplementary Appendix 1 (see the "Availability of Companion Documents" field) for specific harms of the recommendations.

Qualifying Statements

Qualifying Statements

- Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions. These recommendations cannot adequately convey all uncertainties and nuances of patient care.
- The ACR is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.
- The views expressed herein are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States Government.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

Patient Resources

Pocket Guide/Reference Cards

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St Clair EW, Tindall E, Miller AS, McAlindon T, American College of Rheumatology. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2016 Jan;68(1):1-25. [160 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Jan

Guideline Developer(s)

American College of Rheumatology - Medical Specialty Society

Source(s) of Funding

American College of Rheumatology (ACR)

Guideline Committee

- Voting Panel
- Core Leadership Team
- Literature Review Team
- Content Panel

Composition of Group That Authored the Guideline

Authors: Jasvinder A. Singh, MBBS, MPH, University of Alabama at Birmingham; Kenneth G. Saag, MD, MSc, University of Alabama at Birmingham; S. Louis Bridges Jr., MD, PhD, University of Alabama at Birmingham; Elie A. Akl, MD, MPH, PhD, American University of Beirut, Beirut, Lebanon, and McMaster University, Hamilton, Ontario, Canada; Raveendhara R. Bannuru, MD, PhD, Tufts Medical Center, Boston, Massachusetts; Matthew C. Sullivan, BA, Tufts Medical Center, Boston, Massachusetts; Elizaveta Vaysbrot, MD, MS, Tufts Medical Center, Boston, Massachusetts; Christine McNaughton, BS, Tufts Medical Center, Boston, Massachusetts; Mikala Osani, BA, Tufts Medical Center, Boston, Massachusetts; Robert H. Shmerling, MD, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Jeffrey R. Curtis, MD, MS, MPH, University of Alabama at Birmingham; Daniel E. Furst, MD, University of California, Los Angeles; Deborah Parks, MD, Washington University School of Medicine, St. Louis, Missouri; Arthur Kavanaugh, MD, University of California, San Diego; James O'Dell, MD, University of Nebraska Medical Center, Omaha; Charles King, MD, North Mississippi Medical Center, Tupelo; Amye Leong, MBA, Healthy Motivation, Santa Barbara, California; Eric L. Matteson, MD, MPH, Mayo Clinic, Rochester, Minnesota; John T. Schousboe, MD, PhD, University of Minnesota and Park Nicollet Clinic, St. Louis Park; Barbara Drevlow, MD, NorthShore University Health System, Evanston, Illinois; Seth Ginsberg, BSc, Global Healthy Living Foundation, New York, New York; James Grober, MD, NorthShore University Health System, Evanston, Illinois; E. William St. Clair, MD, Duke University Medical Center, Durham, North Carolina; Elizabeth Tindall, MD, Rheumatology Consultants of Oregon, West Linn; Amy S. Miller, American College of Rheumatology, Atlanta, Georgia; Timothy McAlindon, MD, MPH, Tufts Medical Center, Boston, Massachusetts

Voting Panel: Arthur Kavanaugh, MD; James O'Dell, MD; Charles King, MD; Amye Leong, MBA; Eric L. Matteson, MD, MPH; John T. Schousboe, MD, PhD; Barbara Drevlow, MD; Seth Ginsberg, BSc; James Grober, MD; E. William St. Clair, MD; Elizabeth Tindall, MD

Core Leadership Team: Jasvinder A. Singh, MBBS, MPH (*Project Principal Investigator*); Kenneth G. Saag, MD, MSc; S. Louis Bridges Jr., MD, PhD; Elie A. Akl, MD, MPH, PhD; Timothy McAlindon, MD, MPH

Literature Review Team: Timothy McAlindon, MD, MPH (*Literature Review Team Principal Investigator*); Raveendhara R. Bannuru, MD, PhD; Matthew C. Sullivan, BA; Elizaveta Vaysbrot, MD, MS; Christine McNaughton, BS; Mikala Osani, BA; Janet Joyce, MLS (Librarian, Ottawa, Ontario, Canada)

Content Panel: Robert H. Shmerling, MD; Jeffrey R. Curtis, MD, MS, MPH; Daniel E. Furst, MD; Deborah Parks, MD

Financial Disclosures/Conflicts of Interest

Disclosures and Management of Conflicts of Interest

In accordance with American College of Rheumatology (ACR) policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) disclosed all relationships in writing at

the beginning, middle, and end of the project. Disclosures were compared against a previously drafted list of "affected companies" (i.e., companies or organizations that were considered reasonably likely to be positively or negatively affected by care delivered in accordance with the guideline) to determine which relationships were considered conflicts of interest for purposes of this project. Individuals whose primary employment (>51% of work time/effort) was with a company that manufactured or sold therapeutics or diagnostics were not eligible to participate.

The project Principal Investigator (JAS) and Literature Review Team Leader (TM) had no relevant conflicts of interest for the full 12 months before this project began, and a majority (>51%) of all guideline development team members, including the Principal Investigator and Literature Review Team Leader, had no relevant conflicts of interest for the duration of the project. A participant who had any relationship with an affected company was counted as conflicted (i.e., toward the allowed threshold) regardless of the type or subject of the relationship. Intellectual conflicts, such as a prior publication or presentation on an rheumatoid arthritis (RA) therapeutic, were recognized as important and were required to be disclosed, but because they were ubiquitous, participants with intellectual conflicts were not counted as conflicted (i.e., toward the allowed threshold) based on their intellectual conflict alone.

Participant disclosures were included in the project plan that was posted online for public comment. In addition, disclosures of all participants were shared with each project participant in writing. At the face-to-face Voting Panel meeting, verbal disclosures were provided before any content discussion. Updated participant disclosures, as well as ACR committee reviewer disclosures, are available [online](#)

Author Disclosures

Dr. Singh has received consulting fees, speaking fees, and/or honoraria from Savient, Allergan, Regeneron, Merz, Iroko, and Bioiberica (less than \$10,000 each) and from Takeda and Dinora (more than \$10,000 each), and has received grant/research support from Horizon. Dr. Saag has received consulting fees, speaking fees, and/or honoraria from Abbott, Amgen, Bayer, Bristol-Myers Squibb, Lilly, Merck, Pfizer, and Roche/Genentech (less than \$10,000 each) and from Ardea/AstraZeneca (more than \$10,000). Dr. Curtis has received consulting fees, speaking fees, and/or honoraria from Pfizer, Bristol-Myers Squibb, Crescendo, and AbbVie (less than \$10,000 each) and from Roche/Genentech, UCB, Janssen, the Consortium of Rheumatology Researchers of North America (CORRONA) registry, and Amgen (more than \$10,000 each). Dr. Furst has received consulting fees, speaking fees, and/or honoraria from AbbVie, Actelion, Amgen, Bristol-Myers Squibb, Cytos, Janssen, Gilead, GlaxoSmithKline, Novartis, Pfizer, Roche/Genentech, and UCB (less than \$10,000 each) and has received research support from AbbVie, Actelion, Amgen, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Novartis, Pfizer, Roche/Genentech, and UCB. Dr. Kavanaugh has received consulting fees, speaking fees, and/or honoraria from Amgen, AbbVie, and Pfizer (less than \$10,000 each) and grant/research support from Amgen, AbbVie, Bristol-Myers Squibb, Janssen, UCB, Roche, and Pfizer. Dr. O'Dell has received consulting fees, speaking fees, and/or honoraria from Medac, Antares, AbbVie, Bristol-Myers Squibb, and Lilly (less than \$10,000 each). Dr. King receives indirect sponsor payments as Medical Director of the North Mississippi Arthritis and Research Center. Ms. Leong has received consulting fees, speaking fees, and/or honoraria from Horizon, GlaxoSmithKline, and Zimmer (less than \$10,000 each). Dr. Matteson receives royalties from UpToDate, and has received grant/research support from Roche, Genentech, Mesoblast, Ardea, Novartis, Sanofi, Centocor, Janssen, Celgene, UCB, and GlaxoSmithKline. Dr. Grober has received consulting fees, speaking fees, and/or honoraria from Medac (less than \$10,000). Dr. St.Clair owns stock or stock options from Bristol-Myers Squibb, Merck, and Proctor & Gamble, receives royalties from UpToDate, and has received grant/research support from Biogen. Dr. McAlindon has received consulting fees, speaking fees, and/or honoraria from Sanofi-Aventis, Samumed, Fidia, Flexion, and McNeil Consumer Healthcare (less than \$10,000 each) and has a patent on an online clinical trial methodology through Boston University Medical School.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, Bridges SL Jr, Chatham WW, Paulus HE, Suarez-Almazor M, Bombardier C, Dougados M, Khanna D, King CM, Leong AL, Matteson EL, Schousboe JT, Moynihan E, Kolba KS, Jain A, Volkmann ER, Agrawal H, Bae S, Mudano AS, Patkar NM, Saag KG. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012 May;64(5):625-39.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the [American College of Rheumatology \(ACR\) Web site](#) .

Availability of Companion Documents

The following are available:

2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Supplementary appendix 1. Evidence report. 177 p. Available from the [American College of Rheumatology \(ACR\) Web site](#) .

2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Supplementary appendix 2. Literature search strategies. 42 p. Available from the [ACR Web site](#) .

2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Supplementary appendix 3. Flow chart of the study selection process. 1 p. Available from the [ACR Web site](#) .

2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Supplementary appendix 4. Dropped record statements. 6 p. Available from the [ACR Web site](#) .

2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Supplementary appendix 5. Executive summary. 7 p. Available from the [ACR Web site](#) .

American College of Rheumatology policy and procedure manual for clinical practice guidelines. Atlanta (GA): American College of Rheumatology; 2015 Jan. 80 p. Available from the [ACR Web site](#) .

In addition, guideline pocket cards are available for purchase on the [ACR Web site](#) .

Patient Resources

The following is available:

Rheumatoid arthritis. Patient resource. 2017. Available in [English](#) and [Spanish](#) from the American College of Rheumatology (ACR) Web site.

In addition, patient information concerning many of the therapeutic agents discussed in this guideline can be found on the [ACR Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and

answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on June 29, 2011. The information was verified by the guideline developer on July 25, 2011. This summary was updated by ECRI Institute on October 12, 2011 following the U.S. Food and Drug Administration (FDA) advisory on Tumor Necrosis Factor-alpha (TNFα) Blockers. This summary was updated by ECRI Institute on July 31, 2012. The updated information was verified by the guideline developer on August 24, 2012. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab). This summary was updated by ECRI Institute on May 2, 2017. The updated information was verified by the guideline developer on May 31, 2017.

This NEATS assessment was completed by ECRI Institute on June 22, 2017. The information was verified by the guideline developer on July 27, 2017.

Copyright Statement

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions.

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouse® (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the [NGC Inclusion Criteria](#).

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.